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ID

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/292,217	04/15/99	GILLIES S	LEX-004

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EXAMINER	
HAMUD, F	
ART UNIT	**PAPER NUMBER**
1647	9

DATE MAILED: 06/26/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File copy

Office Action Summary

Application No.	Applicant(s)
09/292,217	Stephen D. Gillies
Examiner	**Group Art Unit**
Fozia Hamud	1646

☒ Responsive to communication(s) filed on *Mar 27, 2000*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-27* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-27* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5, 6, 7*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Claims 1-27 are pending and under consideration by the Examiner.

Claim objections

2. Claim 10 is objected to because of the following informalities:

Claim 10 is objected to as using improper/incomplete Markush language. (See M.P.E.P. 706.03(y).) The claim recites ".... wherein the cytokine of the immunoconjugate is selected from the group consisting of aTNF, an interleukin, a GSF and a lymphokine", however, lymphokine is a genus subject matter, and all the cytokines recited in the claim are species of said genus.

Claim rejections-Double patenting

Non-statutory double patenting rejection (obviousness-type)

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3a. Claims 1-27 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-27 of copending Application No. 09/293,042. Although the conflicting claims are not identical, they are not patentably distinct from each other. Instant claims 1-27 are drawn to a method of inducing a cytocidal immune response against a preselected cell type in a mammal, said method comprising administering to said mammal: I) an immunoconjugate comprising an antibody binding site capable of binding to said cell and a cytokine that is capable of inducing a cytocidal immune response against said cell, and ii) an angiogenesis inhibitor, and a composition comprising in combination, an immunoconjugate which comprises an antibody and a cytokine and an angiogenesis inhibitor, while claims 1-27 of 09/293,042 application are drawn to, a method of inducing a cytocidal immune response against a preselected cell type in a mammal, said method comprising administering to said mammal: I) an immunoconjugate comprising antibody binding site capable of binding to said cell and a cytokine that is capable of inducing a cytocidal immune response against said cell, and ii) a prostaglandin inhibitor, and a composition comprising in combination, an immunoconjugate which comprises an antibody and a cytokine and a prostaglandin inhibitor. The only differences between the two applications is, instant claims are drawn to a method of co administering an immunoconjugate and an angiogenesis inhibitor, and the claims of 09/293,042 are drawn to a method of co adminstering an immunoconjugate and a prostaglandin inhibitor. Thus instant claims are directed to a genus subject matter which encompasses the subject matter claimed in 09/293,042 as species. The instant claims are obvious from the claims

of 09/293,042 because angiogenesis inhibitors (claimed in the instant application) are directed to genus subject matter in which the claims of 09/293,042 (prostaglandin inhibitors) are one specific embodiment. It would have been obvious to one of ordinary skill in the art at the time the present invention was made to devise a method of inducing an immune response against a targeted cell by administering a composition comprising an immunoconjuagte which comprises an antibody specific for said cell and a cytokine capable of inducing said immune response against said cell and an angiogenesis inhibitor, because 09/293,042 discloses that prostaglandin inhibitors also include inhibitors of tumor angiogenesis, a process intimately related to COX-2 expression and prostaglandin synthesis, (page 21, lines 4-8).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 U.S.C. § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4a.. Claims 1-27, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising in combination, an immunoconjugate comprising antibody binding site capable of binding to a solid tumor cell and a cytokine that is capable of inducing an immune response against said tumor cell and a prostaglandin inhibitor, and a method of inducing a cytocidal immune response against solid tumor cells in a mammal, said method comprising administering to said mammal: I) an immunoconjugate comprising antibody binding site capable of

binding to said tumor cell and a cytokine that is capable of inducing said immune response against said tumor cell, and ii) a prostaglandin inhibitor, is not enabling for a composition comprising in combination, an immunoconjugate comprising antibody binding site capable of binding to "all" possible preselected cell- types and a cytokine that is capable of inducing an immune response against "all" possible preselected cell types, and a prostaglandin inhibitor, or a method of inducing a cytocidal immune response against "all" preselected cell-types, or against "all" cancer cells, or against a virus-infected cell, by administering an immunoconjugate comprising antibody binding site capable of binding to said cells and a cytokine that is capable of killing said tumor cell, and ii) a prostaglandin inhibitor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claims 1-3, 12, 20 and 27 currently drafted encompass a method of inducing a cytocidal immune response against "all" preselected cell types or against "all" cancer cells, or against a virus-infected cell in a mammal, by administering an immunoconjugate comprising antibody binding site capable of binding to said cells and a cytokine that is capable of inducing an immune response against said cells, and ii) a prostaglandin inhibitor, however, the specification discloses that large solid tumors are much more refractory to antibody mediated therapeutic intervention and to immune therapies than are disseminated metastatic foci, because the production of sufficient immunosuppressive factors to modulate an immune response against the tumors by the metastatic foci (page 10, lines 1-5). The specification also discloses that female mice with palpable tumors were treated with combination therapy comprising KS-IL-2 and a prostaglandin inhibitor (IL-12, endostatin or indomethacin) and in all cases showed that treatment with the antibody-cytokine fusion protein and the prostaglandin

inhibitor was superior to treatment with either agent alone, (see examples 3-5, on pages 35-38). Thus the specification is enabling only for a composition comprising in combination, an immunoconjugate which comprises antibody binding site capable of binding to a solid tumor cell and a cytokine that is capable of inducing a cytocidal immune response against said tumor cell and a prostaglandin inhibitor, and a method of inducing a cytocidal immune response against solid tumor cells in a mammal, said method comprising administering to said mammal: I) an immunoconjugate which comprises antibody binding site capable of binding to said tumor cell and a cytokine that is capable of inducing a cytocidal immune response against said tumor cell, and ii) a prostaglandin inhibitor. The instant specification contemplates that the claimed combination therapy might be effective against a virus-infected cell, for example in HIV infection, (page 10, last paragraph), however, it does not demonstrate that the claimed combination therapy is in fact effective against a virus-infected cell, therefore the instant application is totally nonenabling for a method of inducing a cytocidal immune response against a virus-infected cell in a mammal, said method comprising administering to said mammal: I) an immunoconjugate comprising antibody binding site capable of binding to said cell and a cytokine that is capable of inducing a cytocidal immune response against said cell, and ii) a prostaglandin inhibitor

With respect to claims 10, 25 and 26 which recite ".....wherein the cytokine is selected from the group consisting of TNF, an interleukin, a colony stimulating factor, and a lymphokine", and claims 11 and 26 which recite "...wherein the prostaglandin inhibitor is selected from the group consisting of cyclooxygenase inhibitor, a retinoid, a cytokine and an inhibitor of tumor angiogenesis", the specification is non-enabling for a combination therapy comprising, an immunoconjugate which comprises an antibody and "all" interleukins, or "all" lymphokines, and "all" possible cytokines as

prostaglandin inhibitor. The specification teaches that a "cytokine" must be capable of stimulating or inducing a cytocidal immune response against the tumor cell, (page 12, middle paragraph), therefore, the interleukin or the lymphokine that is part of the immunoconjugate must be able to elicit said response. With respect to the limitation in claim 11 wherein a cytokine can be used as a prostaglandin inhibitor, all cytokines do not function as prostaglandin inhibitor, the specification discloses that IL-12 inhibits angiogenesis through IFN-γ dependent mechanism, therefore, the instant specification is only enabling for IL-12 as a prostaglandin inhibitor. By application of the factors set forth in Ex parte Forman (230 USPQ 546 (Bd. Pat. App. & Int. 1986), and reiterated in In re Wands (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)), which include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims, in the instant application, the quantity of experimentation to determine if the combination therapy using an immunoconjugate which comprises antibody binding site capable of binding to a solid tumor cell and a cytokine that is capable of inducing a cytocidal immune response against said tumor cell and a prostaglandin inhibitor, would be effective against "all" possible preselected cells, or against "all" types of cancer cells, including disseminated metastatic foci or against a virus infected cell which are encompassed by the scope of the claims is practically infinite and the guidance provided in the specification very little. Therefore, absent further guidance from the specification, it would require undue experimentation to determine if the claimed combination therapy would be effective against all cancer cells, including brain cancer cells, against all viral infected cells or against all types of

preselected cells, normal or otherwise. It also would require undue experimentation to determine if an immunoconjugate which comprises an antibody and "all" interleukins, or "all" lymphokines, and "all" possible cytokines as prostaglandin inhibitor or all tumor angiogeneses inhibitors would be effective against preselected cell types.

Claims 4-9, 13-19 and 21-24 are rejected under 35 U.S.C. 112, first paragraph insofar as they depend on claims 1, 12 and 20 for the limitations set forth directly above.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5a. Claims 1-2, 4-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gillies (WO 92/08495) in view of O'Reilly, (January, 1997).

Gillies teaches an immunoconjugate comprising an antibody having a specificity for a surface antigen on a targeted cell and a cytokine, said immunoconjugate retains the antigen binding activity of the immunoglobulin and the biological activity of the cytokine and can be used to specifically deliver the cytokine to the target cell (page 4, first paragraph). The immunoconjugate taught by Gillies comprises a cytokine and an immunoglobulin variable region which is derived from an antibody specific for the target antigen and constant regions which include CH1, CH2 and CH3 domains, (page 11, last paragraph). The immunoconjugate taught by Gillies is be produced by constructing a gene

construct in a 5' to 3' orientation, which comprises a DNA segment encoding a heavy variable chain, a DNA segment encoding the heavy chain constant region and a DNA coding for the cytokine, (page 10, third paragraph). The immunoconjugate taught by Gillies is used to deliver selectively a cytokine to a target cell in vivo so that the cyokine can exert a localized biological effect such as a local inflammatory response or antibody-dependent cellular cytotoxicity (ADCC), and can be used in a method of treating cancer by targeted lysis, (page 14, third paragraph and bottom of page 6). However, Gillies does not teach a composition comprising in combination, an immunoconjugate which comprises an antibody binding site capable of binding to a targeted cell and a cytokine that is capable of inducing an immune response against said cell, and an angiogenesis inhibitor, or a method of inducing a cytocidal immune response against targeted cells in a mammal by administering said composition.

O'Reilly et al teach that endostatin is a specific inhibitor of endothelial proliferation and a potent angiogenesis inhibitor, (see abstract and page 277, last paragraph of column 2). The researchers treated Lewis lung carcinoma metastases systemically with recombinant mouse endostatin, and showed that the growth of metastases was almost completely suppressed compared to mice treated with saline, (see page 279, top of column 2). O'Reilly et al also showed that systemic administration of recombinant mouse endostatin potently suppressed the growth of Lewis lung primary tumors and that increased doses of endostatin were associated with improved efficacy, (see page 280, column 1 and figure 4 on the same page). In other experiments O'Reilly et al implanted mice with several malignant tumors, including B16F10 melanoma, T241 fibrosarcoma and EOMA hemangioendothelioma and demonstrated that all of the tumors rapidly regressed after treatment with

endostatin and that there was no evidence of any toxicity in any of the treated, mice, (page 280, bottom of column 1 and column 2 and figure 7 on page 281). The researchers conclude that systemic administration of recombinant endostatin potently inhibits angiogenesis, maintains metastases at microscopic size and regresses primary tumors to less than 1 mm^3 , a reduction of 150-fold, (page 281, column 2).

Therefore, it would have been obvious to one of ordinary skill in the art at the time that the instant invention was made, to combine the immunoconjugate taught by Gillies et al and the angiogenesis inhibitor taught by O'Reilly et al in a method of inducing a cytocidal immune response against a targeted tumor cell, because Gillies teaches that an immunoconjugate comprising an antibody having a specificity for a surface antigen on a targeted cell (such as a tumor cell) and a cytokine can be used to specifically deliver the cytokine to the target cell so that the cytokine can exert a localized biological effect, such as a local immune response or ADCC, and O'Reilly et al teach that endostatin a specific inhibitor of endothelial proliferation, potently inhibits angiogenesis, thereby, reducing tumor size. One of ordinary skill in the art would have been motivated to use the immunoconjugate comprising an antibody and a cytokine taught by Gillies and the angiogeneses inhibitor taught by O'Reilly et al in a method of inducing a cytocidal immune response against a tumor cell because tumors have two distinct cell populations, a tumor cell population and an endothelial cell population, each of which can stimulate growth of the other, therefore, combined treatment of both cell populations may be better than treatment of either cell population alone.

5b. Claims 1, 11 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gillies (WO 92/08495) in view of O'Reilly, (October, 1994) or Brooks et al (December, 1994) or Ingber et al (December, 1994).

The teachings of Gillies have been set forth directly above in paragraph 5a of this office action, however, Gillies does not teach a composition comprising in combination, an immunoconjugate which comprises an antibody binding site capable of binding to a targeted cell and a cytokine that is capable of inducing an immune response against said cell, and an angiogenesis inhibitor, wherein the angiogenesis inhibitor is selected from the group consisting of, angiostatin, fumagillin and integrin$\alpha v\beta_3$ antagonist, or a method of inducing a cytocidal immune response against targeted cells in a mammal by administering said composition.

O'Reilly et al teach that human angiostatin inhibits angiogenesis over a concentration range of 0.1-100 μg/embryo in the chick embryo chorioallantoic membrane assay (CAM, an assay used for the detection of angiogenesis inhibition), (page 321, column 1). O'Reilly et al teach that treatment of mice with angiostatin suppressed growth of metastases and resulted in 18-fold reduction in the number of metastases, compared to mice treated with saline, and that the majority of metastases treated with angiostatin contained no new vessels compared to control mice which were highly neovascularized, (page 320, column 2 and figure 12b and 12c).

Brooks et al teach that tumor induced angiogenesis is inhibited by an antagonist of integrin$\alpha v\beta_3$, (abstract). The researchers placed fragments of human melanoma or carcinomas of the lung, pancreas and larynx on CAMs of 10-day-old embryos, and intravenously injected the embryos with PBS or anti-integrin$\alpha v\beta_3$ (MAb LM609) and allowed tumors to propagate for an additional 6

days. The authors showed that the MAb LM609 not only prevented the growth of tumors, but induced extensive regression in most cases, (page 1158, column 1 and figure 2).

Ingber et al teach that purified fumagillin inhibited endothelial cell proliferation *in vitro* and tumor-induced angiogenesis *in vivo*, (abstract). The authors demonstrated that fumagillin inhibited angiogensis in the chorioallantoic membrane model at concentration of fumagillin 2 μg per chorioallantoic membrane, and that it suppressed tumor-induced neovascularization in the mouse dorsal air sac, page 555, column 2 and figure 1).

Therefore, it would have been obvious to one of ordinary skill in the art at the time that the instant invention was made, to combine the immunoconjugate taught by Gillies et al and any one of the angiogenesis inhibitors taught by O'Reilly et al, Brooks et al or Ingber et al, in a method of inducing a cytocidal immune response against a targeted tumor cell, because Gillies teaches that an immunoconjugate comprising an antibody having a specificity for a surface antigen on a targeted cell (such as a tumor cell) and a cytokine can be used to specifically deliver the cytokine to the target cell so that the cytokine can exert a localized biological effect, such as a local immune response or ADCC, and all the other three references (i.e O'Reilly et al, Brooks et al and Ingber et al), teach that angiogenesis inhibitors (angiostatin, fumagillin and integrin$\alpha v\beta_3$ antagonist) inhibit tumor-induced angiogenesis and cause regression of tumors. One of ordinary skill in the art would have been motivated to use the immunoconjugate comprising an antibody and a cytokine taught by Gillies and the angiogeneses inhibitors taught by O'Reilly et al, Brooks et al or Ingber et al, in a method of inducing a cytocidal immune response against a tumor cell because tumors have two distinct cell populations, a tumor cell population and an endothelial cell population, each of which can stimulate

growth of the other, therefore, combined treatment of both cell populations may be better than treatment of either cell population alone.

Conclusion

No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fozia Hamud whose telephone number is (703) 308-8896. The examiner can normally be reached on Monday-Friday from 8:00AM to 4:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4227. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Fozia Hamud
Patent Examiner
Art Unit 1646
June 12, 2000

Prema Mertz
PREMA MERTZ
PRIMARY EXAMINER